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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/380,327	09/03/1999	SARAH ANNE ROBERTSON	A20-005	2475

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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 10/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/380,327	ROBERTSON ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *105-140* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *105-140* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/15/04 has been entered.

2. Claims 105-140 are pending and are being acted upon in this Office Action.

3. Claim 135 is objected to because "A" should have been "The" for said dependent claim.

4. The drawings, filed on 9/3/99, stand not in compliance with 37CFR 1.84(a). Please see attached PTO 948 mailed 3/14/01. Appropriate correction is required. It is noted that formal drawings will be submitted at a later time prior to or at payment of the issue fee. It is noted that Applicants will submit them in due course but no later than at the time of payment of the issue fee.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 105-140 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a method of treating recurrent miscarriage by inducing immune tolerance to a paternal antigen of a mammalian prospective mother lacking said immune tolerance, said method comprising administering to a mucosal surface of said prospective mother to a) semen or an MHC Class I antigen on the sperm of a prospective father capable of eliciting a Th-1 response; and b) a substantially purified TGFβ selected from the group consisting of TGFβ1, TGFβ2, and TGFβ3, wherein the said MHC Class I antigen is one which is present on the sperm in seminal plasma of said prospective father; and wherein the exposure is at a time and in an amount effective to induce said immune tolerance, **does not** reasonably provide enablement for any method of treating all infertility such as miscarriage, spontaneous abortion, preeclampsia, early embryonic loss and implantation failure by inducing immune tolerance to any paternal

antigen in a mammalian prospective mother lacking said immune tolerance, said method comprising exposing a mucosal surface of said prospective mother to a) any MHC Class I antigen of a prospective father capable of eliciting a Th-1 response; and b) a substantially purified TGFβ selected from the group consisting of TGFβ1, TGFβ2, and TGFβ3, wherein the said MHC Class I antigen is one which is present on "leukocytes" of said prospective father; and wherein the exposure is at a time and in an amount effective to induce said immune tolerance as set forth in claims 105-114, 116-119, and 124-140. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The scope of the claimed method encompasses treating all infertility (claim 105) such as miscarriage, spontaneous abortion, preeclampsia, early embryonic loss and implantation failure by inducing immune tolerance to all paternal antigens such as MHC class I antigens represent on leukocytes or semen in all population of mammalian prospective mother rather than a specific set of population by exposing a mucosal surface of said prospective mother to all MHC class antigen on leukocytes or in seminal plasma.

The specification discloses only a method of increasing fetal and placental weight by immunizing Balb/cF1 female mice with only CBA sperm with TGFβ1 or without TGFβ1 as a control, two weeks before mating with intact CBA male studs (Example 4). The specification further discloses a method of increasing pregnancy rates by semen exposure around the time of thawed embryo transfer on in vitro fertilization to reduce the risk of early embryonic loss compared to those prospective mother abstain from coitus. The specification also discloses that over the past 20 years, the predominant attempt to modified women's immune response by injecting women with paternal leukocytes in the hope of achieving "tolerance" to paternal antigens but met with limited success (See page 11, first paragraph).

The specification does not teach how to treat all infertility such as miscarriage, spontaneous abortion, preeclampsia, early embryonic loss and implantation failure by exposing female with any MHC Class I antigen on leukocytes and TGFbeta.

Ober et al teach injecting prospective mother with her partner's white blood cells (leukocyte) supposedly to prime her immune system into accepting a fetus bearing his antigen (immune tolerance) does not improve pregnancy outcome in women suffering unexplained recurrent miscarriage (See abstract, in particular).

Worldwide collaborative observational study (AJRI 32: 55-72, 1994) on allogenic leukocyte immunotherapy for recurrent spontaneous abortion or recurrent miscarriage immunotherapy shows that infertility such as recurrent spontaneous abortion is a common complication of pregnancy for which there is no known cure. Published results from controlled clinical trials of allogeneic leukocyte immunization of women with partner's leukocyte have given conflicting results (See abstract, in particular).

Pearson et al teach that there is concerned that rogue clinics may exploit preliminary results to offer couples therapies that have yet to be proved safe and effective. Pearson et al further teaches with each researcher advocating their favored mechanism for sustaining gestation, it will be some time before a complete picture emerges (See enclosed article).

There is insufficient in vivo working example in the specification as filed demonstrating that the claimed method is effective in treating all infertility such as miscarriage, spontaneous abortion, preeclampsia, early embryonic loss and implantation failure, much less about inducing immune tolerance in female by exposing a mucosal surface of said prospective mother to "leukocytes" expressing MHC Class I antigen and TGFβ such as TGFβ1, TGFβ2, and TGFβ3.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments and the declaration of David Alexander Clark under USC § Rule 132 filed 7/15/04 have been fully considered but are not found persuasive.

Applicants' position is that (1) the attached declaration by David A. Clark shows human TGFβ3 significantly reduced the proportion of miscarriage in the CBA x DBA/2 mouse model of recurrent miscarriage, a result which was statistically significant. See attached Clark Dec. at 17-21. Moreover, Dr. Clark further states that these tests provide additional support for the interchangeability of the three TGFβ isoforms. See Clark Dec. at 21.

In response, the scope of the claimed method encompasses treating all infertility (claim 105) such as miscarriage, spontaneous abortion, preeclampsia, early embryonic loss and implantation failure by inducing immune tolerance to all paternal antigens such as MHC class I antigens represent on leukocytes or semen in all population of mammalian prospective mother rather than a specific set of population by exposing a mucosal surface of said prospective mother to all MHC class antigen on leukocytes or in seminal plasma. The data in the declaration by David A. Clark shows that administering human TGFβ3 either before or after mating (sperm) significantly reduced recurrent miscarriage in the CBA x DBA/2 mouse. Applicants assert that the results show of TGF-β3 is interchangeable with TGF-β1 and TGF-β2 in the claimed method.

The specification discloses only a method of increasing fetal and placental weight by immunizing Balb/cF1 female mice with only CBA sperm with TGFβ1 or without TGFβ1 as a control, two weeks before mating with intact CBA male studs (Example 4). The specification further discloses a method of increasing pregnancy rates by semen exposure around the time of thawed embryo transfer on in vitro fertilization to reduce the risk of early embryonic loss compared to those prospective mother abstain from coitus. The specification also discloses that over the past 20 years, the predominant attempt to modified women's immune response by injecting women with paternal leukocytes in the hope of achieving "tolerance" to paternal antigens but met with limited success (See page 11, first paragraph).

The specification does not teach how to treat all infertility such as miscarriage, spontaneous abortion, preeclampsia, early embryonic loss and implantation failure by exposing female with any MHC Class I antigen on leukocytes and TGFbeta.

Ober et al teach injecting prospective mother with her partner's white blood cells (leukocyte) supposedly to prime her immune system into accepting a fetus bearing his antigen (immune tolerance) does not improve pregnancy outcome in women suffering unexplained recurrent miscarriage (See abstract, in particular).

Worldwide collaborative observational study on allogenic leukocyte immunotherapy for recurrent spontaneous abortion or recurrent miscarriage immunotherapy shows that infertility such as recurrent spontaneous abortion is a common complication of pregnancy for which there is no known cure. Published results from controlled clinical trials of allogeneic leukocyte immunization of women with partner's leukocyte have given conflicting results (See abstract, in particular).

Pearson et al teach that there is concerned that rogue clinics may exploit preliminary results to offer couples therapies that have yet to be proved safe and effective. Pearson et al further teaches with each researcher advocating their favored mechanism for sustaining gestation, it will be some time before a complete picture emerges (See enclosed article).

There is insufficient in vivo working example in the specification as filed demonstrating that the claimed method is effective in treating all infertility such as miscarriage, spontaneous abortion, preeclampsia, early embryonic loss and implantation failure, much less about inducing immune tolerance in female by exposing a mucosal surface of said prospective mother to "leukocytes" expressing MHC Class I antigen and TGFβ such as TGFβ1, TGFβ2, and TGFβ3.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:
(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 105-125, and 127-140 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,395,825 (of record, May 1995; PTO 1449) in view of Lea et al (Am J Reprod Immunol 34(1): 52-64, July 1995; PTO 892), Nocera *et al* (Am J. Reprod. Immunology 33: 282-291, 1995; PTO 892), Clark *et al* (of record, Hum Reprod 9(12): 2270-7, Dec 1994, PTO 892), Thomas *et al* (Am J Reprod. Immunol 6(4): 185-9, Dec 1984; PTO 892), Thaler *et al* (Am J Reprod Immunol 21(3-4): 147-50, Nov-Dec 1989; PTO 892) and Prakash *et al* (Reproductive Immunology 70: 403-412, 1981; PTO 892).

The '825 patent teaches a method of treating infertility such as early embryonic loss, implantation failure, spontaneous abortion and preeclampsia associated with IVF in human by administering TGFβ, such as TGFβ1, TGFβ2, TGFβ3, and TGFβ4 (See column 5, line 9-11, in particular) along with antigens such as **sperm** into the reproductive track (genital mucosal surface) of the a female to bolster the chances that a pregnancy will be sustained by increasing the success rate of implantation (See column 5 line 9-12, claim 4 of '825 patent, in particular). The reference TGFβ may be administered either before, after or simultaneously with the male antigens such sperms of the prospective father which are known to express MHC class I molecule on the surface (sperm antigens) and antigens from the conceptus to the mucosal surface wherein the mucosal surface is the reproductive tract of a female (See claims 1-5; column 6 line 67 bridging column 7 line 23; column 4, line 12-21, in particular). The reference TGFβ may be administered by intravenous injection (systemic contact), patch, and gels that are slow release (See column 5, line 1-2; column 6, line 45-55, in particular). The '825 patent further teaches a method of diagnosing or testing the presence of active and/or immunological TGFβ in female or diagnosing mammals with infertility due to inadequate TGFβ (See column 6, line 8-16, column 3, lines 59-65, in particular). The reference method also can be used in conjunction with assisted reproduction such as IVF (See column 3 lines 66 bridging column 4, lines 6, in particular). The '825 patent teaches that TGFβ stimulates the production of trophoblast fibronectin for increasing the success rate of implantation (See entire document, Claims of 825 patent, in particular).

The claimed invention in claim 105 differs from the teachings of the reference only in that the method of treating infertility by inducing immune tolerance by exposing mucosal surface of prospective mother with semen or MHC class I antigen of a prospective father capable of eliciting a Th-1 response and substantially purified TGFbeta.

Lea *et al* teach infertile patients with recurrent spontaneous abortion is deficient in TGFβ2 producing suppressor cells in uterine tissue near the placental attachment site (See abstract, in particular).

Nocera *et al* teach human seminal plasma contains both transforming growth factor-β (TGFβ) such as TGF-β1 and TGF-β2 and is biologically activated from high molecular weight latent TGFβ by acid pH environment of female lower genital tract. Activation of seminal plasma TGFβ may immunologically protect the integrity of sperm (See abstract, in particular) and a reduced level of the seminal plasma TGF-β may potentially render the spermatozoa immunogenic and lead to the attack by the lymphocytes and other immune cells of the female host (See page 290 paragraph bridging col. 1 and 2, in particular). Nocera et al further teach TGF-β has been shown to inhibit the generation and killing activity of IL-2 activated NK cell (LAK) (See page 283, col. 1, par. 2, in particular).

Clark *et al* teach that bioactive TGFβ is known to suppress the generation of cytotoxic cells in vitro and has immunosuppressive activity in vivo during the first trimester pregnancy in humans (See abstract, in particular).

Thomas *et al* teach seminal plasma abrogates the postcoital T cell response to spermatozoal histocompatibility antigens (See abstract, in particular).

Thaler *et al* teach seminal plasma regulates maternal immunity for insemination and pregnancy. Seminal plasma contains factors that specifically suppressive the effects on female alloimmune response to paternally derived alloantigens and could prime mothers prior to fertilization for pregnancy acceptance and is supported by improved implantation rates in controlled clinical trials using timed vaginal exposure to semen during in vitro fertilization or gamete intrafallopian transfer treatment cycle (See abstract, in particular).

Prakash *et al* teach exposing genital mucosal surface of prospective mother to semen through coitus in the form of ejaculate is a form of immunization. During coitus, the female receives in her reproductive tract (mucosal surface) semen from a genetically dissimilar male. The semen contains immunogenic autoantigens, alloantigens, sperm proteins and seminal plasma adsorbed on sperm surface which are highly immunogenic. However, the female reproductive tract does not appear to be an immunologically privileged site. A potent inhibitor of immune response was indeed found in semen (See page 405, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to treat infertility by inducing immune tolerance to a paternal antigen by

exposing the female genital mucosal surface of the prospective mother to semen in the form of ejaculate of the prospective father as taught by Prakash *et al*, Thaler *et al*, and Thomas *et al* along with immunosuppressive factor derived from seminal plasma such as TGFβ1 or TGFβ2 that suppresses postcoital T cell response as taught by Thomas, prime mothers prior to fertilization for pregnancy acceptance which is supported by improved implantation rates in controlled clinical trials using timed vaginal exposure to semen during in vitro fertilization or gamete intrafallopian transfer treatment cycle as taught by Thaler et al, and increasing the success rate of implantation for treatment of infertility such as early embryonic loss, implantation failure, spontaneous abortion and preeclampsia associated with IVF as taught by the '825 patent.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Lea *et al* teach infertile patients with recurrent spontaneous abortion is deficient in TGFβ2 producing suppressor cells in uterine tissue near the placental attachment site (See abstract, in particular). The '825 patent teaches that TGFβ stimulates the production of trophoblast fibronectin for increasing the success rate of implantation (See entire document, Claims of 825 patent, in particular). Clark *et al* teach bioactive TGFβ is known to suppress the generation of cytotoxic T cells in vitro and has immunosuppressive activity that leads to induction of tolerance in vivo during the first trimester pregnancy in humans (See abstract, in particular). Nocera *et al* teach human seminal plasma contains both transforming growth factor-β (TGFβ) such as TGF-β1 and TGF-β2 and TGF-β1 and TGF-β2 are biologically activated from high molecular weight latent TGFβ by acid pH environment of female lower genital tract. Thaler *et al* teach seminal plasma contains factors that specifically suppressive the effects on female alloimmune response to paternally derived alloantigens and could prime mothers prior to fertilization for pregnancy acceptance and is supported by improved implantation rates in controlled clinical trials using timed vaginal exposure to semen during in vitro fertilization or gamete intrafallopian transfer treatment cycle (See abstract, in particular). Claims 107-111 are included in this rejection because the recitation of administering systemically TGFβ and one or more antigens or TGFβ and one or more antigens each administered at a first site and a different site is an obvious variation of the teaching of the '825 patent since the '825 patent teaches that TGFβ can be administered simultaneously, before or after the antigen and the sites of administration is within the purview of one ordinary skilled in that art at the time the invention was made. Claim 124 is included in this rejection because it is an obvious variation of the TGFβ since Nocera *et al* teach human transforming growth factor-β (TGFβ) such as TGF-β1 and TGF-

β2 are biologically activated from high molecular weight latent TGFβ by acid pH environment of female lower genital tract or plasmin. The recitation of active form is within the teachings of '825 patent because administering TGFβ and antigens lead to increase the success rate of implantation, which is the active form of TGFβ (See entire document, Claims of 825 patent, in particular). Claims 127-131 are included in this rejection because the recitation of multiple exposure and dosing schedule to TGFβ and semen or MHC class I antigen of the prospective father prior to attempted conception is within the purview of one of ordinary skilled in the art based on the teachings of the '825 patent. Claims 115 and 120-123 are included in this rejection because it is well within the purview of one of ordinary skill in the medicinal art to optimize doses for the particular treatment regimen. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

Applicants' arguments and the declaration of David Alexander Clark under USC § Rule 132 filed 7/15/04 have been fully considered but are not found persuasive.

Applicants' position is that (1) Feinberg US patent 5,395,825 clearly does not disclose or suggest the main element of the resent claims, namely a method of treating infertility by inducing specific immune tolerance to a paternal antigen in a mammalian prospective mother lacking said immune tolerance. The focus of Feinberg patent was developing methods for achieving improved implantation. (2) The states of the prior art at the time of the present invention actually taught away from the invention so that one of ordinary skill in this art would not have thought that the present method would achieve the desired result. (3) Prior to 1997 it was known that activation of latent TGFβ by trophoblasts inhibited trophoblast migration (Graham et al, (Localization of transforming growth factor-β at the human fetal-maternal interface: role in trophoblast growth and differentiation. Biol. Reprod. 1992,.46:561-572). Indeed, fibrin/fibronectin inhibits trophoblast migration. Prior to 1997 it was also known that reduced trophoblast migration was a characteristic of the histopathology of first trimester miscarriages and of pre-eclampsia (Khong TY et al.: Defective haemochorial placentation as a cause of miscarriage: a preliminary study. Brit. J. Obstet. Gynaec. 1987,94:649-655). Copies of these publications are now shown to me and annexed hereto as Exhibits DAC-1 and DAC-2. (4) although Chaouat et al found that CB/J anti-BALB/c serum could confer protection against abortions in DBA/2 mated CBA/J mice, they admitted that the experiments, in which spleen cells from different strains of mice did or did not absorb out the protective activity. Antibodies to H-2d induced in CBA/J females by immunizing

with DBA/2 cells in this paper did not confer protection. Chaouat did not indicate that there was any requirement that the BALB/c splenocytes were male cells; female BALB/c cells worked just as well.

In response, the arguments with respect to Chaouat et al reference are moot in view of the new rejection. It is agreed upon that the Feinberg US patent 5,395,825 clearly does not disclose a method of treating infertility by inducing specific immune tolerance to a paternal antigen in a mammalian prospective mother lacking said immune tolerance. However, Lea *et al* teach infertile patients with recurrent spontaneous abortion is deficient in TGFβ2 producing suppressor cells in uterine tissue near the placental attachment site (See abstract, in particular).

Nocera *et al* teach human seminal plasma contains both transforming growth factor-β (TGFβ) such as TGF-β1 and TGF-β2 and is biologically activated from high molecular weight latent TGFβ by acid pH environment of female lower genital tract. Activation of seminal plasma TGFβ may immunologically protect the integrity of sperm (See abstract, in particular) and a reduced level of the seminal plasma TGF-β may potentially render the spermatozoa immunogenic and lead to the attack by the lymphocytes and other immune cells of the female host (See page 290 paragraph bridging col. 1 and 2, in particular). Nocera et al further teach TGF-β has been shown to inhibit the generation and killing activity of IL-2 activated NK cell (LAK) (See page 283, col. 1, par. 2, in particular).

Clark *et al* teach that bioactive TGFβ is known to suppress the generation of cytotoxic cells in vitro and has immunosuppressive activity in vivo during the first trimester pregnancy in humans (See abstract, in particular).

Thomas *et al* teach seminal plasma abrogates the postcoital T cell response to spermatozoal histocompatibility antigens (See abstract, in particular).

Thaler *et al* teach seminal plasma regulates maternal immunity for insemination and pregnancy. Seminal plasma contains factors that specifically suppressive the effects on female alloimmune response to paternally derived alloantigens and could prime mothers prior to fertilization for pregnancy acceptance and is supported by improved implantation rates in controlled clinical trials using timed vaginal exposure to semen during in vitro fertilization or gamete intrafallopian transfer treatment cycle (See abstract, in particular).

Prakash *et al* teach exposing genital mucosal surface of prospective mother to semen through coitus in the form of ejaculate is a form of immunization. During coitus, the female receives in her reproductive tract (mucosal surface) semen from a genetically dissimilar male.

The semen contains immunogenic autoantigens, alloantigens, sperm proteins and seminal plasma adsorbed on sperm surface which are highly immunogenic. However, the female reproductive tract does not appear to be an immunologically privileged site. A potent inhibitor of immune response was indeed found in semen (See page 405, in particular). Applicants are referred to the rejection stated above.

In contrast to applicants' assertion that prior to 1997, administering TGFβ that reduced trophoblast migration (Graham et al, (Localization of transforming growth factor-β at the human fetal-maternal interface: role in trophoblast growth and differentiation. Biol. Reprod. 1992,.46:561-572) was a characteristic of the histopathology of first trimester miscarriages and of pre-eclampsia (Khong TY et al.: Defective haemochorial placentation as a cause of miscarriage: a preliminary study. Brit. J. Obstet. Gynaec. 1987,94:649-655), Graham et al reference does not teach reduced trophoblast migration. Graham et al teach TGFβ inhibits first trimester trophoblast proliferation and induces differentiation of trophoblast at the fetal-maternal interface. Graham et al reference is silent that TGFβ reduced trophoblast *migration.* Likewise, Khong et al is silent that treatment of TGFβ causes first trimester miscarriages and pre-eclampsia. Khong et al merely compares the defect of placental bed in idiopathic sporadic and recurrent miscarriage. Khong et al note that defective haemochorial placentation (defective uteroplacental vasculature or inadequate maternal vascular response) is associated with miscarriage as evident by placental bed biopsy from missed miscarriage at 10 weeks there is a paucity of migratory interstitial trophoblast in the deciduas despite the presence of anchoring willi with a thick rim of cytotrophoblast.

Clark *et al* teach that bioactive TGFβ is known to suppress the generation of cytotoxic cells in vitro and has immunosuppressive activity in vivo during the first trimester pregnancy in humans (See abstract, in particular). Cytotoxic T cells are associated with Th1 immune response.

10. Claims 113 and 114 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,395,825 (of record, May 1995; PTO 1449) in view of Lea *et al* (Am J Reprod Immunol 34(1): 52-64, July 1995; PTO 892), Nocera *et al* (Am J. Reprod. Immunology 33: 282-291, 1995; PTO 892), Clark *et al* (of record, Hum Reprod 9(12): 2270-7, Dec 1994, PTO 892), Thomas *et al* (Am J Reprod. Immunol 6(4): 185-9, Dec 1984; PTO 892), Thaler *et al* (Am J Reprod Immunol 21(3-4): 147-50, Nov-Dec 1989; PTO 892) and Prakash *et al* (Reproductive Immunology 70: 403-412, 1981; PTO 892) as applied to claims 105-114, 116-119, 124-125, 127, and 132-140 and further in view of Harlow *et al* (of record, in A Laboratory Manual, Cold Spring Harbor Laboratory, page

61, 1988; PTO 892), World Health Organization (of record, in World Health Organization Laboratory Manual for the Examination of Human Semen and Semen Cervical Mucus Interaction, Cambridge University Press, NY 1987, PTO 892) and Martin-Villa *et al* (of record, Biol Reprod 55(3): 620-9, Sept 1996; PTO 892).

The combined teachings of the '825 patent, Lea *et al*, Nocera *et al,* Clark *et al*, Thaler *et al,* and Prakash *et al* have been discussed supra.

The claimed invention as recited in claim 113 differs from the teachings of the references only in that the method wherein the semen or MHC Class I antigen is presented in purified form instead of semi-purified form.

The claimed invention as recited in claim 114 differs from the teachings of the references only in that the method wherein the purified semen on an inert or adjuvant carrier.

Harlow *et al* teach a simple method of purifying any protein antigen by polyacrylamide gels electrophoresis (See page 61, in particular). Harlow *et al* having pure antigen provides the best case for the production of antibodies.

The WHO Laboratory Manual for the Examination of Human Semen and Semen Cervical Mucus Interaction teaches a method of determining and purifying sperm of a prospective father's ejaculate (See page 5, page 9, Counting the spermatozoa, in particular) and various methods of determining male infertility.

Martin-Villa *et al* teach a method of purifying sperm in semen and determining antigen density such as HLA on cell surface using double labeling cytofluorometry and relevant antibody and HLA-bearing spermatozoa are more capacitated for fertilization than those do not bear HLA (See entire document, Abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to purify MHC class I antigen as taught by Harlow *et al,* the WHO laboratory manual and Martin-Villa et al using the antigens from the sperm or conceptus as taught by the '285 for a method of treating infertility by induction of tolerance to paternal antigen as taught by the '825 patent, Lea *et al*, Nocera *et al,* Clark *et al*, Thaler *et al,* and Prakash *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Harlow *et al* teach purifying any protein antigen by polyacrylamide gels electrophoresis is a simple method (See page 61, in particular). The WHO Laboratory

Manual for the Examination of Human Semen and Semen Cervical Mucus Interaction teaches a method of determining sperm count of a prospective father's ejaculate is useful for (See page 5, page 9, Counting the spermatozoa, in particular) determining male infertility. Martin-Villa *et al* teach a method of purifying sperm in semen and determining antigen density such as HLA on cell surface using double labeling cytofluorometry using relevant antibody and HLA-bearing spermatozoa are more capacitated for fertilization than those do not bear HLA, as one of the indicator for male fertility (See entire document, Abstract, in particular).

11. Claim 126 is rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,395,825 (of record, May 1995; IDS) in view of Lea *et al* (Am J Reprod Immunol 34(1): 52-64, July 1995; PTO 892), Nocera *et al* (Am J. Reprod. Immunology 33: 282-291, 1995; PTO 892), Clark *et al* (of record, Hum Reprod 9(12): 2270-7, Dec 1994, PTO 892), Thomas *et al* (Am J Reprod. Immunol 6(4): 185-9, Dec 1984; PTO 892), Thaler *et al* (Am J Reprod Immunol 21(3-4): 147-50, Nov-Dec 1989; PTO 892) and Prakash *et al* (Reproductive Immunology 70: 403-412, 1981; PTO 892) as applied to claims 105-114, 116-119, 124-125, 127, and 132-140 and further in view of Grainger *et al* (Nat Med 1(9): 932-7, Sep1995; PTO 892).

The combined teachings of the '825 patent, Lea *et al*, Nocera *et al,* Clark *et al*, Thaler *et al,* and Prakash *et al* have been discussed supra.

The claimed invention as recited in claim 126 differs from the combined teachings of the references only in that the method of treating infertility includes administration of plasmin as to increase the level of active TGFβ.

Grainger *et al* teach transforming growth factor beta 1 (TGF-beta 1) is a platelet-derived cytokine and human whole platelets is a rich source of inactive TGF-beta 1, which can be activate by plasmin (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the active TGF beta as taught by the '825 patent for the unpurified form using a biological source rich in TGFβ such as the platelets along with plasmin to activate the inactive form of TGFβ as taught by Grainger *et al* for a method of eliciting an immune reaction in a prospective mammalian mother comprising exposing said prospective mother to one or more antigens of said prospective father and substantially purified TGFβ, said mother leading to tolerance to one or more antigens and alleviation of symptoms of infertility condition as taught by the '825 patent, Lea *et al*, Nocera *et al,* Clark *et al*, Thaler *et al,* and

Prakash *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Grainger *et al* teach platelet is a rich of inactive TGFβ and which can be activate by plasmin (See abstract, in particular).

12. Claim 133 is rejected under 35 U.S.C. 103(a) as being unpatentable over in view of Lea *et al* (Am J Reprod Immunol 34(1): 52-64, July 1995; PTO 892), Nocera *et al* (Am J. Reprod. Immunology 33: 282-291, 1995; PTO 892), Clark *et al* (of record, Hum Reprod 9(12): 2270-7, Dec 1994, PTO 892), Thomas *et al* (Am J Reprod. Immunol 6(4): 185-9, Dec 1984; PTO 892), Thaler *et al* (Am J Reprod Immunol 21(3-4): 147-50, Nov-Dec 1989; PTO 892) and Prakash *et al* (Reproductive Immunology 70: 403-412, 1981; PTO 892) as applied to claims 105-114, 116-119, 124-125, 127, and 132-140 and further in view of Heidenreich *et al* (Am J Reprod Immunol 31(2-3): 69-76, Mar-Apr 1994; PTO 892).

The combined teachings of the '825 patent, Lea *et al*, Nocera *et al,* Clark *et al*, Thaler *et al,* and Prakash *et al* have been discussed supra.

The claimed invention as recited in claim 133 differs from the teaching of the combined references only in that the method of treating infertility includes testing whether anti-sperm antibodies exist.

Heidenreich *et al* teach a method of detecting anti-sperm antibody in infertile male using a highly sensitive and reproducible ELISA assay (See abstract, in particular). The reference assay synchron ELISA (Synelisa) is highly sensitive and reproducible since the assay does not require fixation of the sperm surface antigens by formaldehyde or glutaraldehyde and the structure of sperm surface antigens is not altered by the fixation process.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the step of diagnosing whether anti-sperm antibodies exist using the assay as taught by Heidenreich *et al* with the method of treating infertility by administering TGFβ and male antigens as taught by the '825 patent, Lea *et al*, Nocera *et al,* Clark *et al*, Thaler *et al,* and Prakash *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Heidenreich *et al* teach anti-sperm antibody is associated with male infertility and the reference assay is useful for is highly sensitive and reproducible since the assay does not require fixation of the sperm surface antigens by formaldehyde or glutaraldehyde and the structure of sperm surface antigens is not altered by the fixation process.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.

15. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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